REMARKS

The Office Action

Claims 1 and 3-54 are pending. Claims 1, 3-11, 17, 19, 20, 23-48, 50, 52, and 54 are under consideration. Claims 1, 3-11, 17, 19, 20, 23-48, 50, 52, and 54 stand rejected for indefiniteness and lack of written description. Claims 1, 3-11, 17, 19, 20, 23-27, 33-36, 42-48, 50, and 52 stand further rejected for anticipation by Cai et al. (Proc Natl Acad Sci USA, 1995, 92:6537; hereafter "Cai"). Claims 1, 3-11, 17, 19, 20, 23-27, 29-48, 50, and 52 stand rejected for obviousness over Cai in view of Hutchens et al. (U.S. Patent No. 6,225,047; hereafter "Hutchens"). Claim 28 stands rejected for obviousness over Cai in view of Hutchens and Cull et al. (Methods in Enzymology 182:147; hereafter "Cull").

Support for the Amendments

Claim 1 has been amended to change the preamble and concluding section. Support for these amendments is found in Figures 1-3. Claim 1 has also been amended to combine steps (c) and (e). Alternatives for formation of the first through sixth products in claims 1, 5, and 6 have been deleted. The limitation "reversibly" recited in claims 1, 5, and 6 is supported in Figure 2, which depicts elution of bound phage, and Figure 6, which depicts elution of bound proteins. The term "species" has been changed to "members" based on the suggestion by the Office: both terms refer to the chemical entities that make up either the library or the various products. The limitation of "one or more" with respect to the first, second, and third arrays in claims 1, 5, and 6 has been deleted, as suggested by

the Office. The dependent claims have also been amended to be consistent with amendments to the independent claim. No new matter has been added.

Interview

Applicant thanks the Examiner and his supervisor for the interview conducted on April 10, 2006. Applicant presents herein arguments and amendments commensurate with those discussed in the interview. In addition, a copy of the presentation made during the interview has been appended to this reply.

New Matter Rejection

Claims 5-7 stand rejected under 35 U.S.C. § 112, first paragraph for reciting new matter. The Office states that the limitation "providing one or more third arrays comprising one or more species from said amplified pooled product" is not supported by the specification. Applicant traverses this rejection.

From a telephonic interview with the previous Examiner, it appears that the basis of the rejection is that the term "third" is not supported by the specification. The phrase objected to by the Office is merely a rewording of the original language of claim 5. The original language was "adhering a portion of said amplified pooled product to a support to provide an array," and the amended claim language is "providing a third array comprising one or more species from said amplified pooled product adhered to a support." The original claim language clearly refers to an array made by adhering to a

support a portion of the amplified pooled product. For clarity, Applicant has now termed this array as the "third array" to simplify reference to this array in further dependent claims, e.g., claim 53. Merely providing a numerical designation of an array is not new matter. Original claim 1 recited step (a) to create an array from a first sample, now referred to as the "first array" and step (b) to create an array from a second sample, now referred to as the "second array." Original claim 5 recited step (i) to create an array from the amplified pooled product, which is neither the first nor the second array. The following table summarizes the three arrays, their contents, and how they were produced.

Summary of Arrays

Array	Chemical Content	Produced From
First	Polypeptides from first sample	First Sample
Second	Polypeptides from second sample	Second Sample
Third	Members of library, e.g., phage	Pooled Second and Fourth Products

Thus, the use of the term "third" does not broaden the scope of the invention, since Applicant was clearly in possession of three arrays in the claims as originally filed, as evidenced by steps (a), (b), and (i). Support for three, different arrays is also found Figure 4, which schematically depicts the three arrays recited in the claims. No new matter has been added, and the rejection may be withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3-11, 17, 19, 20, 23-48, 50, 52, and 54 stand rejected for indefiniteness. The purpose of the definiteness requirement is to ensure that "the scope of the claim is clear to a hypothetical person possessing the ordinary skill in the pertinent art" (M.P.E.P. § 2171). The instant claims meet this standard. Each of the bases for the rejection is considered in turn.

With respect to recitation of "one or more first[/second] arrays comprising one or more polypeptides from a first[/second] complex biological sample adhered to a support," the language objected to has been deleted as discussed with the Examiner, and the rejection is moot. For the avoidance of doubt, we note that different physical arrays may be employed in steps c, d, and e, see claims 48-52.

With respect to the library employed in previous step (e), the libraries employed in previous steps (c) and step (e) are different aliquots of the same library, i.e., they contain the same chemical entities. As suggested by the Office, claim 1 has now been amended to combine steps (c) and (e), and the rejection may be withdrawn.

With respect to the term "species," Applicant has amended the claims to replace this term with "members," i.e., the chemical entities, e.g., phage, that make up the library. For clarity, "peptide-nucleic acid" is defined in the specification and used herein to describe the link between a peptide and the nucleic acid that encodes it, and this term is not a reference to nucleobases linked by a peptide backbone, i.e., PNAs.

With respect to the rejection of the terms first through sixth products, the Office states that "it is not clear whether these products are peptides, nucleic acids, or the combination." Applicant believes that the interview has clarified the identity of the products recited in the claims. The following table summarizes each of the first through sixth products including the type of chemical species that make up each product and the manner in which each product is made.

Summary of Products

Product	Chemical Content	Produced From
First	Members of peptide-nucleic acid coupled library, e.g., phage	Binding of peptides in the library to the first array
Second	Members of peptide-nucleic acid coupled from library, e.g., phage	Peptides of the first product that do not bind to the second array
Third	Members of peptide-nucleic acid coupled from library, e.g., phage	Binding of peptides in the library to the second array
Fourth	Members of peptide-nucleic acid coupled from library, e.g., phage	Peptides of the third product that do not bind to the first array
Fifth	Polypeptides from first or second sample	Polypeptides of the first or second sample that bind to the third array
Sixth	Polypeptides from sample not used in fifth product	Polypeptides of the other sample that bind to the third array

For further clarity, claim 1 has been amended to correspond to one embodiment of the invention in which the first product includes members of the library that reversibly bind to the first array, and the third product includes members of the library that reversibly bind

of the first product that do not bind to the second array, and the fourth product includes member of the third product that do not bind to the first array. The second and fourth products may also be used to separate or isolate the polypeptides that are differentially expressed between the two samples. For example, the second and fourth products may be pooled, amplified, and adhered to a support to form a third array. The polypeptides in the first or second sample and the third array are then used to create the fifth product, and the polypeptides in the sample not used to make the fifth product are used with the third array to create the sixth product. Since the claimed methods are screening methods, the specific compounds present in each of the first through sixth products will necessarily depend on both the samples being screened and the specific library used to probe the samples.

Claim 1 was further rejected for omitting a step of identifying a polypeptide, and the Office has requested clarification of the amendments previously made by Applicant. As discussed in the interview, the preamble to claim 1 has now been amended to recite "identifying differences in expression of polypeptides between two samples" and also to indicate that the contents of the second and fourth products are members of the library that bind to polypeptides that are relatively overexpressed in the first or second sample.

Applicants have amended the instant claims and provided arguments to address the indefiniteness rejections, and the rejection may be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1-11, 17, 19, 20, 23-48, 50, and 52 stand further rejected for failing to comply with the written description requirement with respect to peptide-nucleic acid coupled library and first through sixth products. The Office indicated in the interview that these rejections will be withdrawn as the instant claims are drawn to screening claims rather than the compounds identified using the claimed methods. For the record, Applicant provides the following arguments to rebut the rejection.

M.P.E.P. § 2163.02 states that "[a]n objective standard for determining compliance with the written description requirement is, 'does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed.'" (citations omitted). Furthermore, M.P.E.P. § 2163 states:

> What is conventional or well known to one of ordinary skill in the art need not be disclosed in detail.... If a skilled artisan would have understood the inventor to be in possession of the the claimed invention at the time of filing, even if every nuance of the claims is not explicitly described in the specification, the adequate description requirement is met. (citations omitted)

A single disclosed species may also be sufficient to adequately support a genus:

> disclosure of a single method of adheringly applying one layer to another was sufficient to support a generic claim to "adheringly applying" because one skilled in the art reading the specification would understand that it is unimportant how the layers are adhered, so long as they are adhered. (M.P.E.P. § 2163; citations omitted).

The instant claims meet the standards for complying with the written description requirements.

In *In re Herschler*, 591 F.2d 693, 697, 200 USPQ 711, 714 (CCPA 1979), recitation of "corticosteroid" provided sufficient written description for "physiologically active steroid" because "use of known chemical compounds in a manner auxiliary to the invention must have a corresponding written description only so specific as to lead one having ordinary skill in the art to that class of compounds" (M.P.E.P. § 2163). The facts of the instant case are analogous to those in *In re Herschler* with respect to the term "peptide-nucleic acid coupled library." The instant case involves the use of research tools including classes of compounds, e.g., phage, that were known in the art prior to the filing date. The specification specifically recites a review article (Li Nature Biotechnology 2000 18:1251) and laboratory manual (Barbas III, et al. Phage Display: A Laboratory Manual Cold Spring Habor Press: Cold Spring Harbor 2001) that describes the well-known nature of peptide-nucleic acid coupled libraries at the time of filing the instant application (page 14). Thus, the instant claims are directed to the use of known classes of compounds, and reference to this class of compounds, coupled with disclosure of a review and laboratory manual on the field and the extensive knowledge in the art at the time of filing provides adequate written description per established precedent of the Court of Appeals for the Federal Circuit.

With respect to the first through sixth products, the claims indicate the type of chemical species that are included in each of these products. The first through fourth products include members from the same peptide-nucleic acid coupled library, the fifth product includes one or more polypeptides from one of the complex biological samples,

and the sixth product includes one or more polypeptides from the other sample. The contents of each of these products will depend on the peptide-nucleic acid coupled library and the samples employed. As the samples vary, so will each of the products. Indeed, it is the contents of these products that are point of the instant invention. The specification provides guidance on the samples and peptide-nucleic acid coupled libraries that may be employed in the instant methods. One skilled in the art would understand that Applicant was in possession of each of these genera because each is produced during the method. This last basis of the rejection should also be withdrawn.

Rejections under 35 U.S.C. § 102

Claims 1, 3-11, 17, 19, 20, 23-27, 33-36, 42-48, 50, 52 and 54 stand rejected for anticipation by Cai. In order to be anticipatory, a reference must teach every limitation of the claims (M.P.E.P. § 2131). Applicants traverse this rejection as applied to the amended claims.

As previously stated, one key feature of the instant methods is that the *same* peptide-nucleic acid coupled library is first independently exposed to polypeptides from two samples. The product of the exposure with one sample is then exposed to the other sample. Thus, in the claimed method, polypeptides from two samples are contacted with an entire peptide-nucleic acid coupled library and also with a subset of the peptide-nucleic acid library that has affinity to another sample. As discussed in the interview, this

method allows for the identification of polypeptides that are relatively overexpressed in both samples. Cai simply does not teach such a method.

As stated in Applicant's previous reply, Cai teaches the following: a phage library is contacted with melanoma cells, and phage that bind to the melanoma cells are eluted and amplified. Thereafter, these eluted phage may be contacted with melanocytes, endothelial cells, and fibroblast cells to eliminate phage that cross react with healthy cells. Finally, individual phage identified by the panning procedure may be tested for binding to a variety of cell lines. Thus, Cai only exposes the melanoma cells to a single phage library and members of the library that were eluted from the same melanoma cells. Cai does not expose the melanoma cells to phage eluted from another sample that was contacted with the entire phage library. Thus, nowhere does Cai teach exposing a peptide-nucleic acid library to two samples, and then exposing the product of that step, i.e., the first and third products, to the other sample, as instantly claimed.

In maintaining the rejection, there appears to have been confusion over the claim scope. As described above, a single library is contacted with two distinct samples, and steps (c) and step (e) have been combined to clarify this point. The Office also states, "And further the unabsorbed phage (refer to step e) of the instant claims) are tested against several different samples, which would refer to the subsequent products of the instant claims." This statement is incorrect. As discussed above, previous step (e) (now part of step (c)) requires the use of a second aliquot of the peptide-nucleic acid coupled library and not "unabsorbed phage" from the second product.

For the record, Applicant also notes that claim 1 recites steps (a) through (d), and none of these steps is optional. For a reference to anticipate this claim, it must disclose each of the claimed steps, and Cai does not. As Cai does not anticipate claim 1, it is unnecessary to consider the rejection of the dependent claims.

Rejections under 35 U.S.C. § 103

Claims 1-11, 17, 19, 20, 23-48, 50, 52 and 54 stand rejected for obviousness over Cai in view of Hutchens or in view of Hutchens and Cull. Applicants traverse this rejection.

To support an obviousness rejection, the Office must put forth a *prima facie* case that meets the legal standard for obviousness found in M.P.E.P. § 2142. This section states:

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure.

This standard has not been met in the present case as the combined references do not teach or suggest the instant claims.

In making the obviousness rejection, the Office acknowledges that it relies on Cai to teach the limitations of claim 1 and that Hutchens and Cull are only cited as teaching or

suggesting limitations in the dependent claims. As stated above, Cai does not teach or suggest the limitations of claim 1. Furthermore, any teachings of Hutchens on using cross-linkers or mass spectrometry or of Cull on preliminary processing of biological samples do not remedy the deficiencies of Cai. Thus, the Office has failed to establish a *prima facie* case of obviousness, and the rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Enclosed is a petition to extend the period for reply for three months, to and including April 19, 2006. If there are any additional charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: April 19, 2006

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Differential Capture Proteomics

Interview for U.S. Application No. 10/022,034

Review of Invention

USPTO

April 10th, 2006

From Genes to Functional Proteins

Genes → mRNAs → Proteins

3×10^4 Species	→	$>10^6$ Species
Most Species Defined	→	<0.2% Known
Most Species Measurable	→	<0.2% with Abs

Limitations of Conventional Proteomics

- 2D gels (industry standard)
  - <2,000 (0.2%) proteins identified and quantified in plasma
- Chromatography/Mass Spectrometry
  - <2,000 (0.2%) proteins identified and quantified in plasma
- GeneProt Inc. (Geneva) tried cataloging plasma/serum
  - 10 liters for each of two samples
  - Chromatography generated 350,000 fractions
  - 51 mass specs, 6 months to complete analysis
- No time- or cost- effective processes
  - After >25 years of extensive efforts and substantial funding
  - Only way for field to progress is through new ideas
  - Motivation for new Differential Capture Proteomics approach

What is Differential Proteomics?

- Most valuable form of proteomics
  - Comparison between Complex Biological Samples
  - Proteins that are Differentially Expressed
    - Healthy versus Diseased
    - Treated with drug versus not-treated with drug
    - Many other important comparisons
- Just knowing which proteins are present not very informative
- Anyway, catalog of all proteins not feasible now
- Need approach without *a priori* knowledge

What is Differential Capture Proteomics?

- Process that Compares Two Complex Biological Samples
- No *a priori* knowledge needed
- Focuses just on Differentially Expressed Proteins
- During process, isolate Affinity Capture Reagents
  - Reagents are from Peptide-Nucleic Acid Coupled Libraries
    e.g., Phage Display Libraries encoding antibodies/peptides
  - "Subtractive Step" removes phage against proteins in common

1. Remaining phage bind only to Differentially Expressed Proteins
2. These phage enable purification of Differentially Expressed Proteins
3. Purified Differentially Expressed Proteins can be characterized and quantified

Example of Differential Capture Proteomics (DCP)

1st Complex Biological Sample eg: "Healthy"

2nd Complex Biological Sample eg: "Diseased"

Differential Capture Process Occurs on a Support

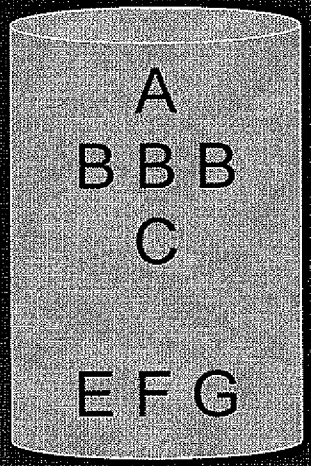
Peptide-Nucleic Acid Coupled Library eg: "Phage Display Peptide Library"

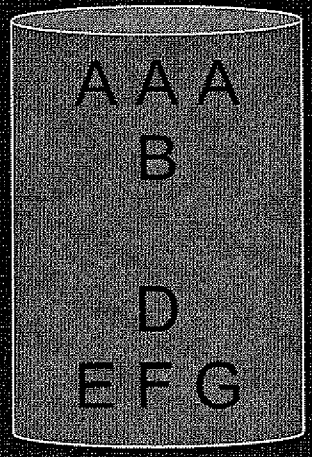
1. Isolate phage which bind to Differentially Expressed Proteins
2. Phage enable purification of Differentially Expressed Proteins
3. Purified Differentially Expressed Proteins can be characterized and quantified

Protein Composition of Two Samples

Samples contain 5 classes of proteins

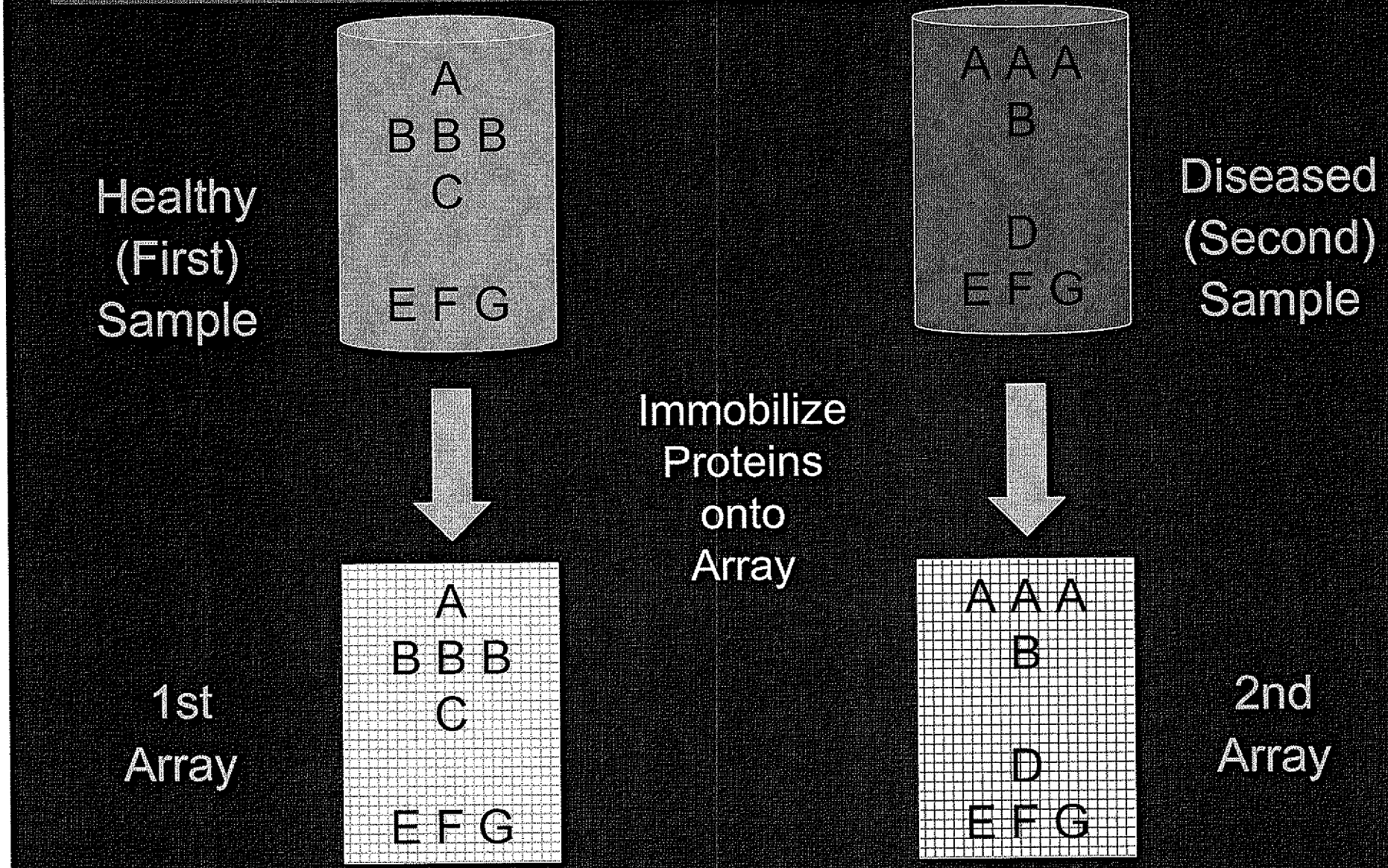
Healthy (First) Sample





Diseased (Second) Sample

DCP *Step 1: Immobilize Proteins on Arrays*



DCP *Step 2: Proteins Capture Phage*

Phage Display Peptide Library
a = Any phage that binds Protein A
Phage species = a, b, c, d, e, f, g, h, i

1. Pass Library over arrays

2. Specific phage bind to epitopes

3. Discard unbound phage

1st Array

Aa
Bb Bb Bb
Cc
Ee Ff Gg

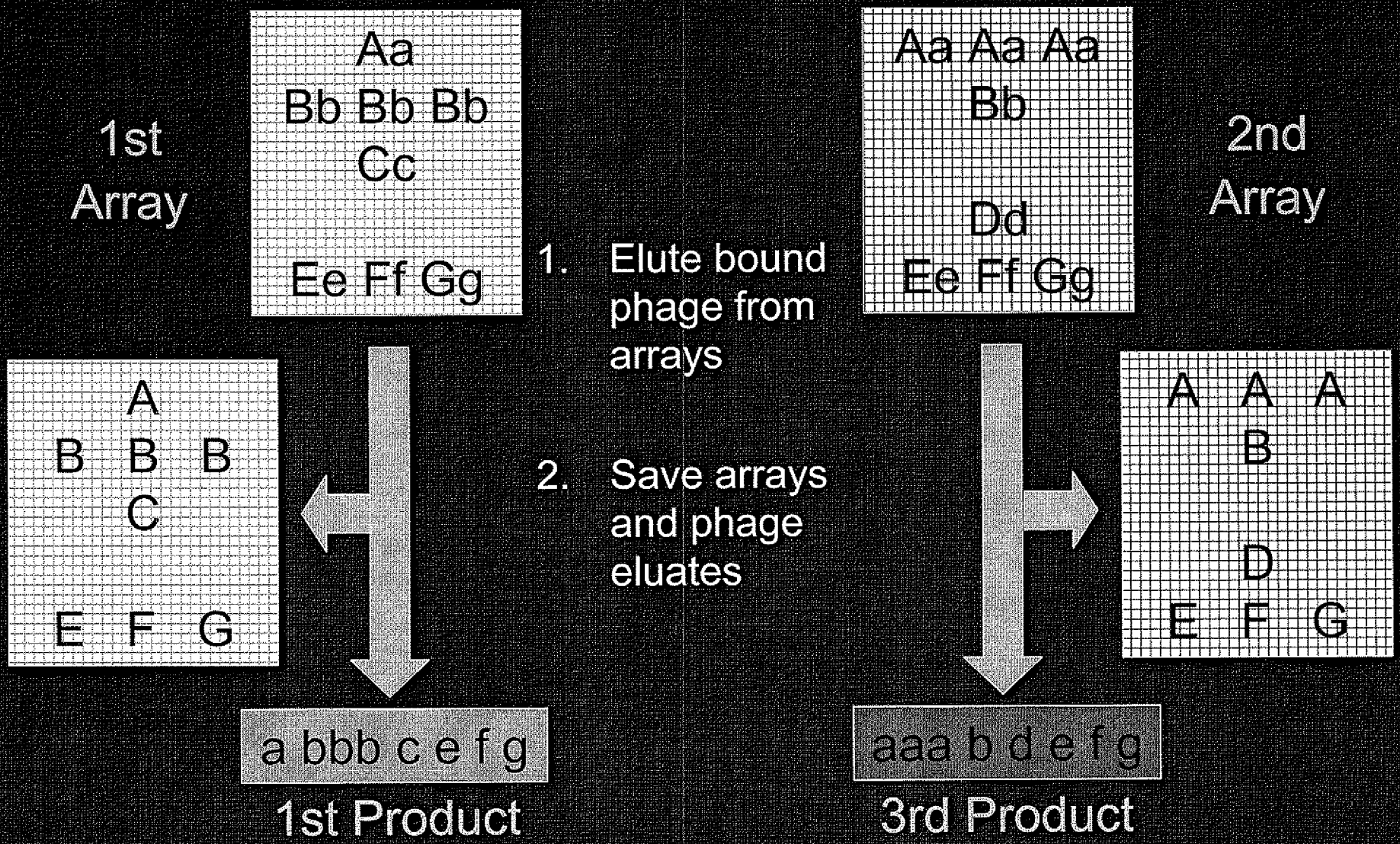
aa d h i

2nd Array

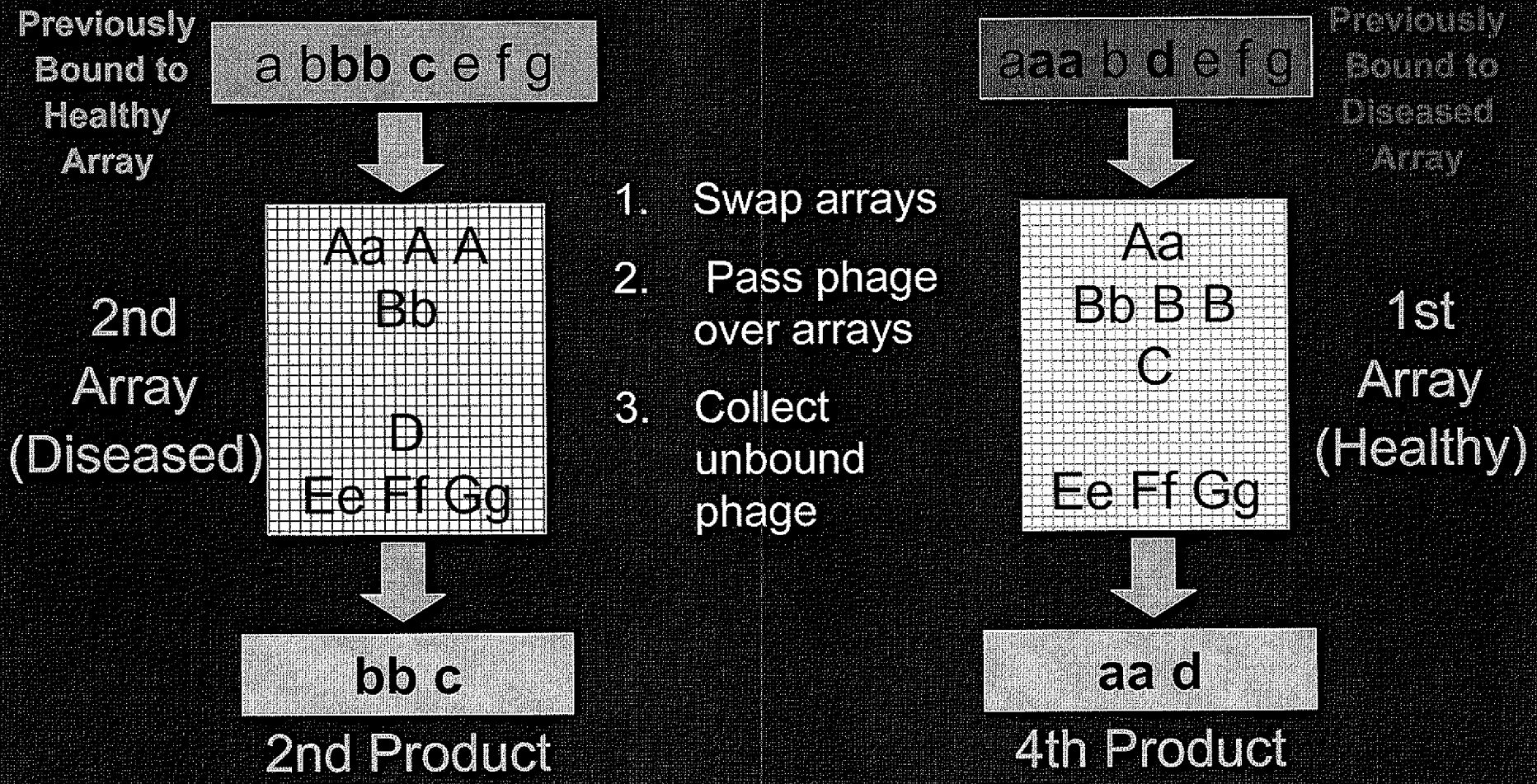
Aa Aa Aa
Bb
Dd
Ee Ff Gg

bb c h i

DCP *Step 3: Elute Phage off Arrays*

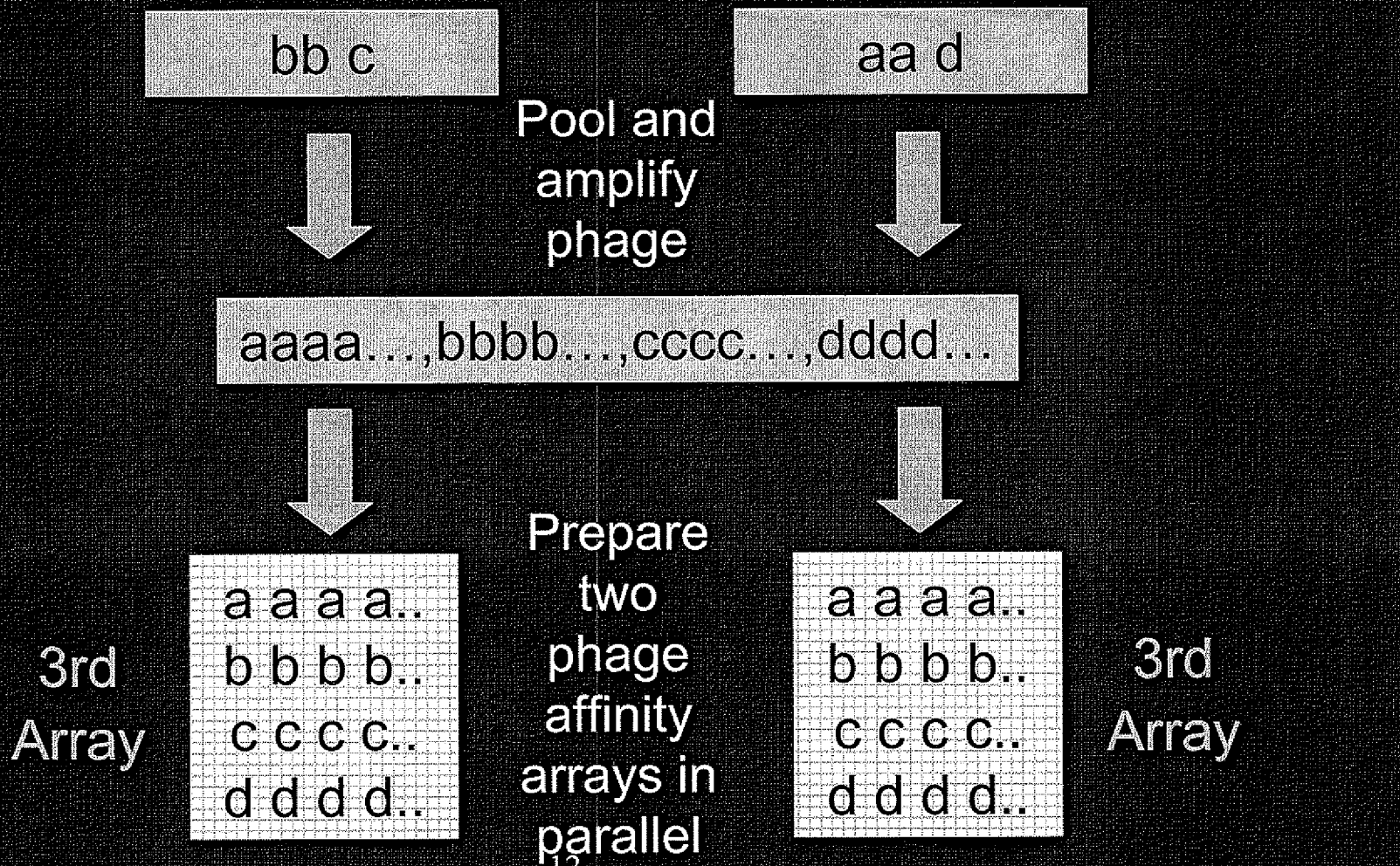


DCP *Step 4: Swap Arrays, Collect Unbound Phage*

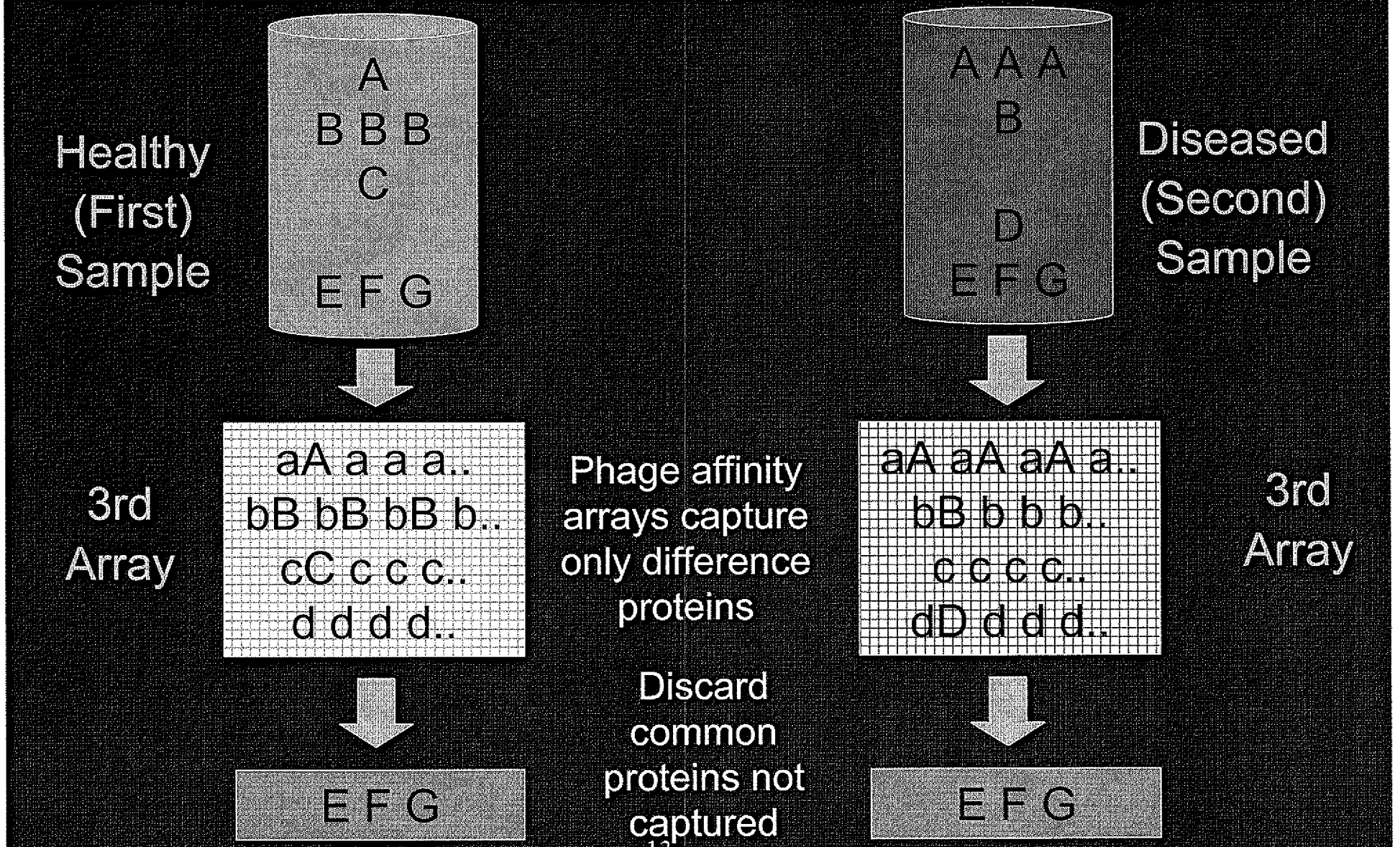


Phage Affinity Reagents against Differentially Expressed Proteins

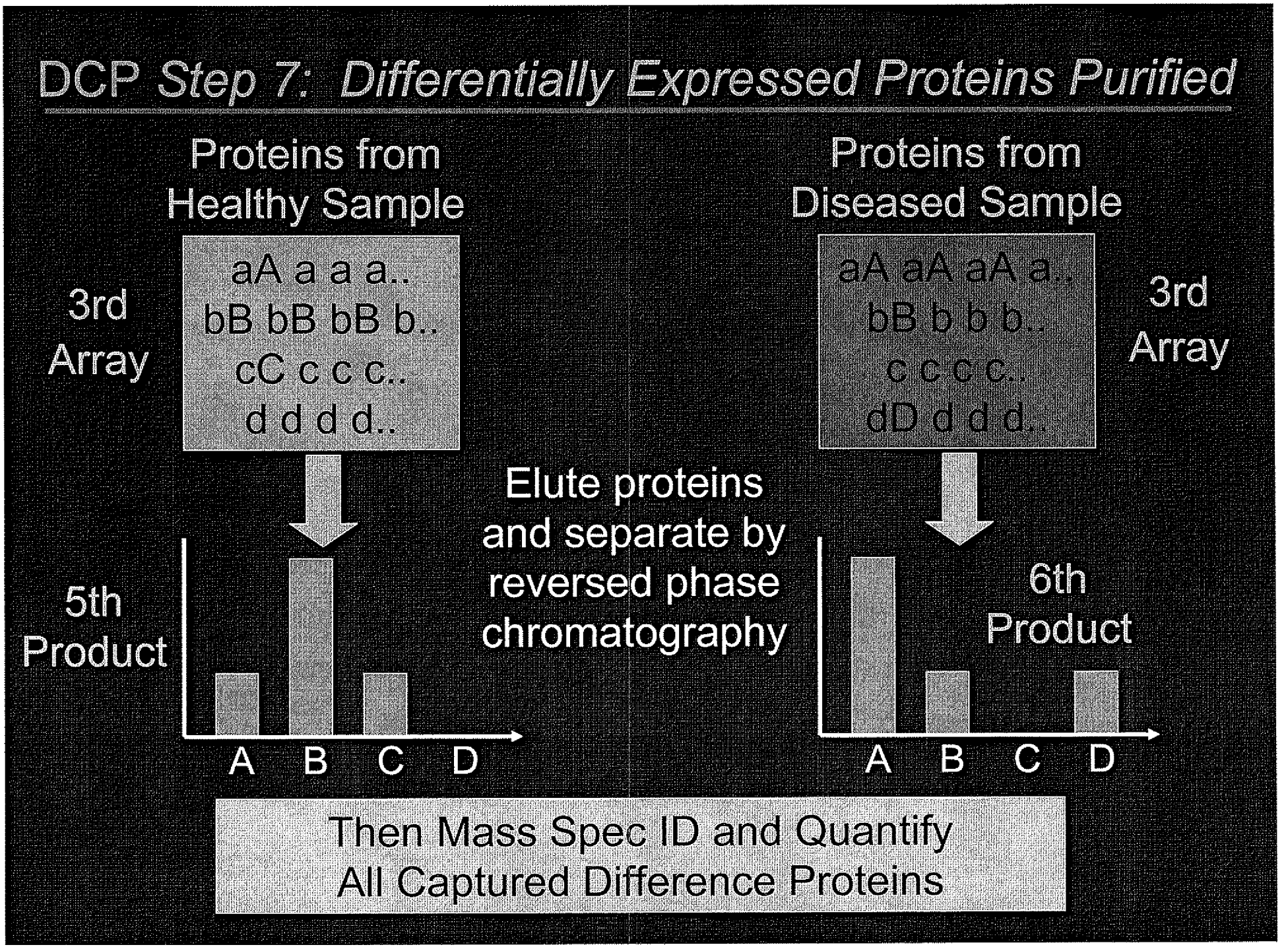
DCP *Step 5: Prepare Phage Affinity Arrays*



DCP *Step 6: Phage Arrays Capture Differentially Expressed Proteins*



DCP *Step 7: Differentially Expressed Proteins Purified*



Output From Differential Capture Proteomics

1st Complex Biological Sample eg: "Healthy"

2nd Complex Biological Sample eg: "Diseased"

Differential Capture Process Occurs on a Support

Peptide-Nucleic Acid Library eg: "Phage Display Peptide Library"

1. Isolate phage which bind to Differentially Expressed Proteins
2. Phage enable purification of Differentially Expressed Proteins
3. Purified Differentially Expressed Proteins can be characterized and quantified

Summary of Differential Capture Process